REMARKS

Claims 1-21 are pending in this application. Claims 22-23 have been withdrawn due to a Restriction Requirement. Claims 1-21 are rejected under 35 USC § 103(a) as being unpatentable over H. HIROSE et al. (Metabolism, 2002) in view of T. TSAO et al., (Journal of Biological Chemistry, 2002), W.H.L. HACKENG et al., (Journal of Clinical Endocrinology and Metabolism, 1986), Y. FURUYA, et al. (International Journal of Urology, 2000), and I. LEMIEUX et. al., (Archives of Internal Medicine, 2001).

The claims have been amended by copying the phrase "within four weeks" from Claim 19 into Claim 1 and the dependent claims that refer to an increase in HMW adiponectin (Claims 1, 3-8, and 13-18).

Applicants respectfully submit that the references cited by the Examiner either separately or as a group do not make the claimed method obviousness.

HIROSE et al.

The primary reference (HIROSE) discloses changes in metabolic parameters, body fat distribution, and serum adiponectin levels in Japanese male patients having type 2 diabetes during treatment with pioglitazone, which is an insulin sensitizer. The patients in the study in HIROSE were treated with pioglitazone for three months, and the measurements of serum adiponectin, glucose, blood pressure, and other parameters were measured at the start of the study and again at the end of the study. After three months of treatment, the author found that serum adiponectin and BMI increased, and glucose and HbA_{1c} decreased. The authors looked for a mathematical correlation between the percent changes in adiponectin and other parameters that were measured in the study. The only parameter that correlated with adiponectin was the change in subutaneous adipose tissue. (See the paragraph bridging pages 315 and 316 of the paper).

The HIROSE publication lacks several important features of the instant claims:

The measurements of adiponectin and other parameters were measured before the study and after three months. There were no measurements within the first 4 weeks of the study, which is the claimed time frame during which the change in adiponectin levels is advantageous for predicting whether serum HbA_{1c} will later be reduced based on clinical measurements which cannot be successfully performed in the early stages of treatment.

The serum glucose and $HbA1_{1c}$ had already been reduced after 3 months of treatment in the HIROSE et al. study. HIROSE et al. also does not disclose HMW adiponectin, LMW adiponectin, or their ratio, as pointed out in the Office Action.

HIROSE et al. does not recognize that the increase in adiponectin may be related to improvements in insulin sensitivity or to reductions in serum glucose. In the second column on page 316, HIROSE et al. stated that adiponectin levels are reported to be low in obese patients and to increase with weight reduction in both diabetic and non-diabetic obese patients. They then suggest four mechanisms that they "speculate" may account for the increase in adiponectin after treatment with pioglitazone despite an increase in BMI (obesity). The second of these mechanisms is that the increase in adiponectin may be "Secondary to changes in glucose control, but it also seems unlikely considering that the change in adiponectin did not correlate with the percent change in FPG, $HbA1_{1c}$, or HOMA-IR…". (see page 316, column 2, first paragraph). HIROSE et al. continues in the next paragraph on page 316, column 2, by suggesting that "an increase in adiponectin levels might be one of the mechanisms by which pioglitazone exerts beneficial effects to prevent atherosclerosis in type 2 diabetic patients…." In the last paragraph of the HIROSE et al. publication, the authors conclude on page 317 with the statement that it is suggested that "pioglitazone may have an anti-atherosclerosis effect by increasing serum adiponectin levels."

The HIROSE et al. reference thus does not in any way suggest that adiponectin might be an early marker (in less than 4 weeks) of whether pioglitazone will be effective in treating type 2 diabetes.

TSAO, et al.

The TSAO et al. publication discloses that Acrp30 exists as different isoforms having different molecular weights. The high molecular weight isoform activates NF-kB, but the low molecular weight isoform does not activate NF-kB. The biological role of NF-kB activation was not known when the paper was written, and there was no evidence that the different isoforms of adiponectin (HMW and LMW) have different effects on diabetes in diabetic patients.

HACKENG, FURUYA AND LEMIEUX

The Examiner cites these references to support the contention that it is obvious to use ratios of HMW to LMW adiponectin or total adiponectin to identify the patients who are responsive to treatment with insulin sensitizers. In these three references, ratios of other biomarkers, such as HDL, LDL and /or total cholesterol, are used as reliable measures for making conclusions about human diseases or health. However, none of these three references deals with isoforms of adiponectin (HMW, LMW), and the Tsao et al. reference deals with the activities of HMW and LMW adiponectin with NF-kB, which is not known to have any relevance to type 2 diabetes. These three references and Tsao et al. do not support a rejection based on prima facie obviousness relating to using ratios of HMW and LMW or total adiponectin to predict the effectiveness of a treatment for type 2 diabetes.

Summary

The Hirose reference does not suggest that adiponectin can be used as a biomarker that will identify whether a type 2 diabetic patient will be a responder to treatment with pioglitazone within the first four weeks of treatment. A patient is a responder or non-responder to treatment based on measurements of hemoglobin A_{1c}, but changes in hemoglobin A_{1c} require more than four weeks of treatment before a decision can be made as to the effectiveness of the treatment based on clinical data. HIROSE et al. has no relevance to the current application because Hirose only provides measurements obtained after three months of measurement. Also, HIROSE et al. viewed adiponectin as a potential biomarker for atherosclerosis, and not for diabetes.

The other four references do not eliminate the deficiencies in HIROSE et al., especially with respect to the initial four week interval in the instant claims. The other four references are alleged to suggest the use of the HMW/LMW ratio as a biomarker for treatment of diabetes, but the references do not provide evidence that HMW adiponectin is active for diabetes, and none of them mention ratios of HMW and LMW or total adiponectin.

These references thus do not suggest the claimed method, and they certainly do not provide a reasonable expectation that the method can be practiced as claimed.

Conclusion

The 35 USC§103(a) rejection should be withdrawn. It is respectfully submitted that the claims are in condition for allowance, which action is earnestly solicited.

If the Examiner wishes to discuss any matter relating to this application, he is invited to telephone the undersigned attorney.

Respectfully submitted,

By _____

James L. McGinnis
Reg. No. 34,387
Attorney for Applicant

MERCK & CO., Inc.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-0641

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